## AMENDMENTS TO THE CLAIMS

Docket No.: 04266/100M275-US1

- 1. (Currently amended) A method of treating neuromuscular dysfunction of the lower urinary tract in a mammal in need of such treatment comprising administering to said mammal an effective amount of a compound having selective affinity for the mGlu5 subtype of the metabotropic glutamate receptors to treat said neuromuscular dysfunction of the lower urinary tract.
- 2. (Previously presented) The method of claim 1 wherein said compound has an at least about 10-fold selectivity for the mGlu5 subtype of the metabotropic glutamate receptors.
- 3. (Currently amended) The method of claim 1 wherein said compound has an at least about 25-fold slectivity selectivity for the mGlu5 subtype of the metabotropic glutamate receptors.
- 4. (Currently amended) The method of claim 1 wherein said compound has an at least about 50-fold sleetivity selectivity for the mGlu5 subtype of the metabotropic glutamate receptors.
- 5. (Currently amended) The method of claim 1 wherein said compound has an at least about 100-fold slectivity selectivity for the mGlu5 subtype of the metabotropic glutamate receptors.
- 6. (Currently amended) The method of claim 1 wherein said compound has an at least about 500-fold slectivity selectivity for the mGlu5 subtype of the metabotropic glutamate receptors.
- 7. (Original) The method of claim 1 wherein said compound is a selective mGlu5 receptor antagonist.
- 8. (Original) The method of claim 7 wherein said neuromuscular dysfunction is urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance, cystitis, incontinence, urine leakage, enuresis, dysuria, urinary hesitancy or difficulty in emptying the bladder.

- 9. (Withdrawn) The method of claim 8 wherein said neuromuscular dysfunction that is decreased urinary compliance is decreased bladder storage capacity.
- 10. (Withdrawn) The method of claim 8 wherein said neuromuscular dysfunction is interstitial cystitis.
- 11. (Original) The method of claim 1 wherein said compound is administered as a pharmaceutically acceptable composition.
- 12. (Original) The method of claim 11 wherein said compound is administered via an oral, parenteral, intranasal, sublingual, rectal or inhalatory route, or by insufflation, transdermal patches or lyophilized composition.
- 13. (Original) The method of claims 1 wherein said compound is administered in an amount of between about 0.01 to about 25 mg/kg/day.
- 14. (Original) The method of claim 13 wherein said compound is administered in an amount of between about 0.1 to about 10 mg/kg/day.
- 15. (Original) The method of claim 14 wherein said compound is administered in an amount of about 0.2 to about 5 mg/kg/day.
- 16. (Original) The method of claim 1 wherein said compound is administered at a total daily dose of about 25 to about 1000 mg.
- 17. (Original) The method of claim 16 wherein said compound is administered at a total daily dose of about 150 to about 500 mg.

- 18. (Original) The method of claim 17 wherein said compound is administered at a total daily dose of about 350 mg.
- 19. (Original) The method of claim 1 wherein said compound is administered in combination with an antimuscarinic drug.
- 20. (Original) The method of claim 19 wherein said antimuscarinic drug is selected from the group consisting of oxybutynin, tolterodine, darifenacin and temiverine.
- 21. (Withdrawn) The method of claim 1 wherein said compound is administered in combination with an  $\alpha$ 1-adrenergic antagonist.
- 22. (Withdrawn) The method of claim 21 wherein said  $\alpha$ 1-adrenergic antagonist is selected from the group consisting of prazosin, doxazosin, terazosin, alfuzosin and tamsulosin.
- 23. (Withdrawn) The method of claim 1 wherein said compound is administered in combination with a 5-HT<sub>1A</sub> receptor antagonist.
- 24. (Withdrawn) The method of claim 1 wherein said compound is administered in combination with a selective COX2 inhibitor.
- 25. (Withdrawn) The method of claim 24 wherein said selective COX2 inhibitor comprises a NO releasing group.
- 26. (Withdrawn) The method of claim 1 wherein said compound is administered in combination with a non-selective COX1/COX2 inhibitor.
- 27. (Withdrawn) The method of claim 26 wherein said non-selective COX1/COX2 inhibitor derivative comprises a NO releasing group.

Application No. 10/768,953 Docket No.: 04266/100M275-US1 Amendment dated April 2, 2007

Reply to Office Action of January 24, 2007

28. (Original) The method of claim 1 wherein said mammal is a human.

29. (Original) The method of claim 1 wherein said compound is administered in admixture with a pharmaceutically acceptable diluent or carrier.

- 30. (Original) The method of claim 29 wherein said pharmaceutically acceptable diluent or carrier is selected from the group consisting of ethanol, water, glycerol, aloe vera gel, allantoin, glycerine, vitamin A oil, vitamin E oil, mineral oil, phosphate buffered saline, PPG2 myristyl propionate, magnesium carbonate, potassium phosphate, vegetable oil, animal oil, and solketal.
- 31. (Withdrawn) The method of claim 1 wherein said compound having selective affinity for the mGlu5 subtype of the metabotropic glutamate receptors has a general formula I

$$R_2$$
 $X_1$ 
 $X_1$ 
 $X_1$ 
 $X_1$ 
 $X_1$ 
 $X_2$ 
 $X_3$ 
 $X_4$ 
 $X_1$ 
 $X_1$ 
 $X_2$ 
 $X_3$ 
 $X_4$ 
 $X_1$ 
 $X_2$ 
 $X_3$ 
 $X_4$ 
 $X_4$ 
 $X_4$ 
 $X_4$ 
 $X_5$ 
 $X_4$ 

wherein:

R<sub>1</sub> represents hydrogen, lower alkyl, lower hydroxyalkyl, lower alkylamino, piperidino, carboxyl, esterified carboxyl, amidated carboxyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, cyano, alkynyl, lower alkoxycarbonyl, di-(lower)alkylamino, lower alkylaminocarbonyl, trifluoromethylphenylaminocarbonyl or N-(lower)alkyl-N-phenylcarbamoyl, said N-(lower)alkyl and N-phenyl radicals being unsubstituted or substituted independently with a substituent selected from the group consisting of lower alkyl, lower alkoxy, halogen, and trifluoromethyl groups,

R<sub>2</sub> represents hydrogen, lower alkyl, carboxyl, esterified carboxyl, amidated carboxyl, lower hydroxyalkyl, hydroxyl, lower alkoxy or lower alkanoyloxy, lower alkoxycarbonyl, di-(lower)-alkylamino-(lower)alkanoyl, di-(lower)alkylaminomethyl, 4-(4-fluorobenzoyl)-piperidin-1-yl-

carbonyl, 4-*tert*-butyloxycarbonylpiperazin-1-yl-carbonyl, 4-(4-azido-2-hydroxybenzoyl)-piperazin-1-yl-carbonyl or 4-(4-azido-2-hydroxy-3-iodo-benzoyl)-piperazin-1-yl-carbonyl,

R<sub>3</sub> represents hydrogen, lower alkyl, carboxy, lower alkoxycarbonyl, lower alkylcarbamoyl, lower hydroxyalkyl, di-(lower)alkylaminomethyl, morpholinocarbonyl or 4-(4-fluorobenzoyl)piperidin-1-yl-carbonyl,

R4 represents hydrogen, lower alkyl, hydroxyl, lower hydroxyalkyl, lower aminoalkyl, (lower)alkylamino(lower)alkyl, di-(lower)-alkylamino(lower)alkyl, unsubstituted or hydroxysubstituted (lower)alkyleneamino(lower)alkyl, lower alkoxy, lower alkanoyloxy, lower aminoalkoxy, (lower)alkylamino(lower)alkoxy, di-(lower)-alkylamino(lower)alkoxy, lower alkoxycarbonyl, carboxy(lower)alkylcarbonyl, (lower)alkoxycarbonyl(lower)alkoxy, lower hydroxyalkyl, m-hydroxy-p-azidophenylcarbonylamino(lower)alkoxy, lower aminoalkoxy, phthalimido(lower)alkoxy, unsubstituted (lower)alkyleneamino(lower)alkoxy or (lower)alkyleneamino(lower)alkoxy substituted with hydroxyl or 2-oxo-imidazolidin-1-yl-groups, carboxyl, esterified carboxyl, amidated carboxyl, lower carboxyalkoxy or lower esterified carboxyalkoxy,

X<sub>I</sub> represents a lower alkenylene, lower haloalkenylene, lower alkynylene or lower haloalkynylene group, wherein each of the foregoing groups is linked via vicinal unsaturated carbon atoms, or an azo group (-N=N-), and

R<sub>5</sub> represents an aromatic or heteroaromatic group which is unsubstituted or substituted with one or more substituents selected from lower hydroxyalkyl, lower alkoxycarbonyl, lower alkanoyl, trifluoromethyl, trifluoromethoxy, trimethylsilylalkynyl, azido, lower aminoalkoxy, di-(lower)-alkylamino(lower)alkoxy, monohalobenzylamino, thienylmethylamino, thienylcarbonylamino, trifluoromethylphenylaminocarbonyl, tetrazolyl, lower alkanoylamino, benzylcarbonylamino, (lower)alkylaminocarbonylamino, (lower)alkoxycarbonylaminocarbonylamino, (lower)alkylsulfonyl, lower alkyl, halo, lower haloalkyl, lower haloalkoxy, lower alkenyl, lower alkynyl, unsubstituted phenyl or phenyl substituted with one or more substituent selected from the group consisting of lower alkyl, lower alkoxy, halo and trifluoromethyl groups, unsubstituent selected from the group consisting of lower alkyl, lower alkoxy, halo and trifluoromethyl groups, hydroxyl,

lower hydroxyalkyl, (lower)alkanoyloxy(lower)alkyl, lower alkoxy, lower alkenyloxy, lower alkylenedioxy, lower alkanoyloxy, lower amin alkoxy, (lower)alkylamino(lower)alkoxy, (lower)alkanoylamino(lower)alkoxy, N-(lower)-alkyl-N-(lower)-alkanoylamino(lower)alkoxy, unsubstituted phenoxy or phenoxy substituted with one or more substituent selected from the group consisting of lower alkyl, lower alkoxy, halo and trifluoromethyl groups, phenyl(lower)alkoxy or phenyl(lower)alkoxy wherein the phenyl group is substituted with one or more substituent selected from the group consisting of lower alkyl, lower alkoxy, halo and trifluoromethyl groups, acyl, carboxyl, esterified carboxyl, amidated carboxyl, cyano, carboxy(lower)alkylamino, esterified carboxy(lower)alkylamino, amidated carboxy(lower)alkylamino, phosphono(lower)alkylamino, esterified phosphono(lower)alkylamino, nitro, amino, lower alkylamino, di-(lower)-alkylamino, acylamino, N-acyl-N-(lower)-alkylamino, phenylamino, phenyl(lower)alkylamino, cycloalkyl(lower)alkylamino or heteroaryl(lower)alkylamino each of which may be unsubstituted or lower alkyl- lower alkoxy-, halo- and/or trifluoromethyl-substituted,

or an enantiomer, diastereoisomer, N-oxide, crystalline form, hydrate, solvate, pharmacologically active metabolite, prodrug, or pharmaceutically acceptable salt thereof.

32. (Withdrawn) The method of claim 31 wherein said compound has a structure wherein X<sub>1</sub> is a (C<sub>2-4</sub>)alkenylene, (C<sub>2-4</sub>)haloalkenylene, (C<sub>2-4</sub>)alkynylene or (C<sub>2-4</sub>)haloalkynylene group, wherein each of the foregoing groups is bonded via vicinal unsaturated carbon atoms;

R<sub>1</sub> is hydrogen, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, hydroxy(C<sub>1-4</sub>)alkyl, cyano, ethynyl, carboxy,  $(C_{1-4})$ alkoxycarbonyl, di $(C_{1-4})$ alkylamino,  $(C_{1-6})$ alkylaminocarbonyl, or trifluoromethylphenylaminocarbonyl;

 $R_2$  is hydrogen, hydroxy,  $(C_{1-4})$  alkyl, hydroxy  $(C_{1-4})$  alkyl,  $(C_{1-4})$  alkoxy, carboxy,  $(C_{2-5})$ alkanoyloxy,  $(C_{1-4})$ alkoxycarbonyl, di $(C_{1-4})$ alkylamino $(C_{1-4})$ alkanoyl, di(C<sub>1-4</sub>)alkylaminomethyl, 4-(4-fluorobenzoyl)-piperidin-1-yl-carbonyl, 4-tert- butyloxycarbonylpiperazin-1-yl-carbonyl, 4-(4-azido-2-hydroxybenzoyl)-piperazin-1-yl-carbonyl or 4-(4-azido-2hydroxy-3-iodobenzoyl)-piperazin-1-yl-carbonyl;

 $R_3$  is hydrogen,  $(C_{1-4})$  alkyl, carboxy,  $(C_{1-4})$ alkoxycarbonyl,  $(C_{1-4})$ alkylcarbamoyl, hydroxy $(C_{1-4})$ alkyl, di $(C_{1-4})$ alkylaminomethyl, morpholinocarbonyl or 4-(4-fluoro-benzoyl)-piperidin-1-yl-carbonyl;

R<sub>4</sub> is hydrogen, hydroxy, (C<sub>1-4</sub>)alkoxy, carboxy, (C<sub>2-5</sub>)alkanoyloxy, (C<sub>1-4</sub>)alkoxycarbonyl, amino(C<sub>1-4</sub>)alkoxy, di(C<sub>1-4</sub>)alkylamino(C<sub>1-4</sub>)alkylamino(C<sub>1-4</sub>)alkyl, carboxy(C<sub>1-4</sub>)alkylcarbonyl, (C<sub>1-4</sub>)alkoxycarbonyl(C<sub>1-4</sub>)alkoxy, hydroxy(C<sub>1-4</sub>)alkyl, di(C<sub>1-4</sub>)alkylamino(C<sub>1-4</sub>)alkoxy, or m-hydroxy-p-azidophenylcarbonylamino (C<sub>1-4</sub>)alkoxy; and R<sub>5</sub> is a group of formula

$$\begin{bmatrix} R_{a} & N & R_{d} & R_{d}$$

wherein

 $R_a$  and  $R_b$  independently are hydrogen, hydroxy, halogen, nitro, cyano, carboxy,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, hydroxy( $C_{1-4}$ )alkyl,  $(C_{1-4})$ alkoxycarbonyl,  $(C_{2-7})$ alkanoyl,  $(C_{2-5})$ alkanoyloxy,  $(C_{2-5})$ alkanoyloxy( $(C_{1-4})$ alkyl, trifluoromethyl, trifluoromethoxy, trimethylsilylethynyl,  $(C_{2-5})$ alkynyl, amino, azido, amino( $(C_{1-4})$ alkoxy,  $(C_{2-5})$ alkanoylamino( $(C_{1-4})$ alkoxy,  $(C_{1-4})$ alkylamino( $(C_{1-4})$ alkylamino, monohalobenzylamino, thienylamino, thienylcarbonylamino, trifluoromethylphenylaminocarbonyl, tetrazolyl,  $(C_{2-5})$ alkanoylamino, benzylcarbonylamino,  $(C_{1-4})$ alkylaminocarbonylamino  $(C_{1-4})$ alkylaminocarbonylamino or  $(C_{1-4})$ alkylsulfonyl;

 $R_c$  is hydrogen, fluorine, chlorine, bromine, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{2-5})$ alkanoyloxy,  $(C_{1-4})$ alkoxy or cyano; and

R<sub>d</sub> is hydrogen, halogen or (C<sub>1-4</sub>)alkyl.

33. (Withdrawn) The method of claim 31 wherein said compound has a structure wherein X<sub>1</sub> is a (C<sub>2-4</sub>)alkenylene, (C<sub>2-4</sub>)haloalkenylene, (C<sub>2-4</sub>)alkynylene or (C<sub>2-4</sub>)haloalkynylene group, wherein each of the foregoing groups is linked via vicinal unsaturated carbon atoms;

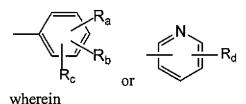
 $R_1$  is hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, cyano, ethynyl or di $(C_{1-4})$ alkylamino;

R<sub>2</sub> is hydrogen, hydroxy, carboxy, (C<sub>1-4</sub>)alkoxycarbonyl, di(C<sub>1-4</sub>)alkylaminomethyl, 4-(4-fluorobenzoyl)-piperidin-1-yl-carbonyl, 4-*tert*-butyloxycarbonyl-piperazin-1-yl-carbonyl, 4-(4-azido-2-hydroxybenzoyl)-piperazin-1-yl-carbonyl or 4-(4-azido-2-hydroxy-3-iodobenzoyl)-piperazin-1-yl-carbonyl;

 $R_3$  is hydrogen,  $(C_{1-4})$ alkyl, carboxy,  $(C_{1-4})$ alkoxycarbonyl,  $(C_{1-4})$ alkylcarbamoyl, hydroxy $(C_{1-4})$ alkyl, di $(C_{1-4})$ alkylaminomethyl, morpholinocarbonyl or 4-(4-fluoro-benzoyl)-piperidin-1-yl-carbonyl;

 $R_4$  is hydrogen, hydroxy, carboxy,  $(C_{2-5})$ alkanoyloxy,  $(C_{1-4})$ alkoxycarbonyl, amino $(C_{1-4})$ alkoxy, di $(C_{1-4})$ alkylamino $(C_{1-4})$ alkylamino $(C_{1-4})$ alkyl; and

R<sub>5</sub> is a group of formula



R<sub>a</sub> and R<sub>b</sub> independently are hydrogen, halogen, nitro, cyano, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, trifluoromethyl, trifluoromethoxy or (C<sub>2-5</sub>)alkynyl;

 $R_c$  is hydrogen, fluorine, chlorine, bromine, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{2-5})$ alkanoyloxy,  $(C_{1-4})$ alkoxy or cyano; and

R<sub>d</sub> is hydrogen, halogen or (C<sub>1-4</sub>)alkyl.

- 34. (Withdrawn) The method of claim 31 wherein said compound is 2-methyl-6-(phenylethynyl)pyridine (MPEP).
- 35. (Withdrawn) The method of claim 31 wherein said compound is 2-methyl-6-(2-phenylethenyl)pyridine (SIB 1893).
  - 36. (Withdrawn) The method of claim 1 wherein said compound has a general formula I-A

Docket No.: 04266/100M275-US1

wherein

R' is hydrogen or (C<sub>1-4</sub>)alkyl and

M is a group of formula

wherein

 $R_{aa}$ ,  $R_{bb}$  and  $R_{cc}$  are independently of each other hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, hydroxyl,  $(C_{1-4})$ hydroxyalkyl, cyano or halo,

R<sub>dd</sub> is cyano or halo,

 $R_{\infty}$  is hydroxyl,  $(C_{1-4})$ alkyl or  $(C_{1-4})$ alkoxy,

R<sub>ff</sub> is hydrogen or (C<sub>1-4</sub>)alkyl,

 $R_{gg}$  and  $R_{hh}$  are hydrogen or together form a group of formula =0, =CH-CN, =N-OH, =N-O-(C<sub>1-4</sub>)alkyl, =CH-PO<sub>3</sub>[(C<sub>1-4</sub>)alkyl]<sub>2</sub> or =CH-CO-R<sub>kk</sub>, wherein  $R_{kk}$  is (C<sub>1-4</sub>)alkoxy or -NR<sub>ll</sub>R<sub>mm</sub>, where  $R_{ll}$  and  $R_{mm}$  are chosen independently from hydrogen, (C<sub>1-4</sub>)alkyl and phenyl,

Rii and Rii are independently hydrogen, (C1-4)alkyl or phenyl, and

 $V_1$  is  $(CH_2)_n$ ,  $CHR_{nn}$ , wherein n is 1, 2 or 3,  $R_{nn}$  is hydroxyl,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy,  $(C_{1-4})$ alkoxy( $C_{1-4}$ )alkoxy( $C_{1-4}$ )alkoxycarbonyl, carbamoyl,  $(C_{1-4})$ alkylcarbamoyl, phenyl, pyridyl, thienyl or  $(R_{oo}, R_{pp})$ N-lower alkyl, wherein  $R_{oo}$  is hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkyl, or, if  $R_{gg}$  and  $R_{hh}$  are each hydrogen,  $V_1$  can also be  $NR_{qq}$ , wherein  $R_{qq}$  is  $(C_{1-4})$ alkoxycarbonyl, benzyloxycarbonyl, benzoyl, thienyl,  $(C_{1-4})$ alkanoyl, carbamoyl, mono- or di- $(C_{1-4})$ -alkylcarbamoyl or phenylcarbamoyl, any phenyl ring in  $R_{qq}$  being optionally substituted by one or more halo, cyano,  $(C_{1-4})$ alkyl or  $(C_{1-4})$ alkoxy groups,

or an enantiomer, diastereoisomer, N-oxide, crystalline form, hydrate, solvate, pharmacologically active metabolite, prodrug, or pharmaceutically acceptable salt thereof.

37. (Withdrawn) The method of claim 1 wherein said compound has a general formula II-A

$$R_8$$
 $R_9$ 
 $R_{10}$ 
 $R_{10}$ 
 $R_{10}$ 
 $R_{10}$ 
 $R_{10}$ 
 $R_{10}$ 

 $R_6$ ,  $R_7$ ,  $R_8$ ,  $R_9$  and  $R_{10}$  represent, independently from each other, hydrogen, lower alkyl, lower alkoxy, -(CH<sub>2</sub>)<sub>n</sub>-halo, -(CH<sub>2</sub>)<sub>n</sub>-NR<sub>e</sub>R<sub>f</sub>, -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>e</sub>)-C(O)-(lower)alkyl, aryl or heteroaryl, which is unsubstituted or substituted by one or more lower alkyl groups;

## B<sub>1</sub> represents

(B1) 
$$R_{11}$$
; (B2)  $R_{15}$ ; (B3)  $R_{19}$ ; (B3)  $R_{19}$ ; (R4)  $R_{17}$ ; (R5)  $R_{21}$ ; (R5)  $R_{21}$ ; (R5)  $R_{21}$ ; (R5)  $R_{22}$ ; (R5)  $R_{21}$ ; (R5)  $R_{22}$ ; (R5)  $R_{22}$ ; (R5)  $R_{23}$ ; (R6)  $R_{30}$ ; (R6)  $R_{30}$ 

wherein

R<sub>11</sub> represents hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sub>e</sub> or halo;

R<sub>12</sub> represents hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sub>f</sub>, halo, nitro or heteroaryl which is unsubstituted or substituted with lower alkyl or cycloalkyl;

 $R_{13}$  represents hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sub>2</sub> or aryl;

R<sub>14</sub> represents lower alkyl;

R<sub>15</sub> represents hydrogen, lower alkyl or halo;

R<sub>16</sub> represents hydrogen or alkyl;

 $R_{17}$  represents -(CH<sub>2</sub>)<sub>n</sub>-N(R<sub>e</sub>)-C(O)-lower alkyl;

R<sub>18</sub> represents hydrogen or lower alkyl;

 $R_{19}$ ,  $R_{20}$ ,  $R_{21}$  and  $R_{22}$  represent, independently from each other, hydrogen, lower alkyl, -  $(CH_2)_n$ -halo or lower alkoxy;

 $R_{23}$ ,  $R_{24}$  and  $R_{25}$  represent, independently from each other, hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-halo or lower alkoxy;

R<sub>26</sub> represents hydrogen or lower alkyl;

R<sub>27</sub> represents hydrogen, lower alkyl or lower alkyl substituted with one or more substituents selected from hydroxy and halo;

R<sub>28</sub> represents hydrogen, lower alkyl, lower alkanoyl or nitro;

R<sub>29</sub>, R<sub>30</sub> and R<sub>31</sub> represent, independently from each other, hydrogen or lower alkyl;

Re, Rf and Rg represent, independently from each other, hydrogen or lower alkyl;

n is 0, 1, 2, 3, 4, 5 or 6;

X2 is -CH2-, -O- or -S-; and

 $Y_1$  is -CH= or -N=;

- 38. (Withdrawn) The method of claim 37 wherein  $B_1$  represents  $B_1$  and  $R_{12}$  represents  $(CH_2)_n$ - $C(O)OR_f$ , unsubstituted heteroaryl or heteroaryl substituted with one or more lower alkyl or cycloalkyl.
  - 39. (Withdrawn) The method of claim 38 wherein R<sub>12</sub> represents -C(O)O-lower alkyl.
- 40. (Withdrawn) The method of claim 1 wherein said compound has general formula II-B or II-C

$$R_{34}$$
  $R_{35}$   $R_{36}$   $R_{36}$   $R_{36}$   $R_{36}$   $R_{37}$   $R_{38}$   $R_{34}$   $R_{35}$   $R_{36}$   $R_{36}$ 

## wherein

 $R_{32}$ ,  $R_{33}$ ,  $R_{34}$ ,  $R_{35}$  and  $R_{36}$  represent, independently from each other, hydrogen, lower alkyl, -  $(CH_2)_n$ -halogen, lower alkoxy, - $(CH_2)_n$ -NR<sub>e</sub>R<sub>f</sub>, - $(CH_2)_n$ -N(R<sub>e</sub>)-C(O)-(lower)alkyl, aryl or heteroaryl which is unsubstituted or substituted by one or more lower alkyl residues;

Docket No.: 04266/100M275-US1

R<sub>37</sub> represents hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sub>e</sub> or halogen;

R<sub>38</sub> represents hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sub>f</sub>, halogen, nitro or heteroaryl which is unsubstituted or substituted with lower alkyl or cycloalkyl;

R<sub>39</sub> represents hydrogen, lower alkyl, -(CH<sub>2</sub>)<sub>n</sub>-OH, -(CH<sub>2</sub>)<sub>n</sub>-C(O)OR<sub>g</sub> or aryl;

R<sub>40</sub> represents lower alkyl;

R<sub>41</sub> represents hydrogen, halogen or lower alkyl; and

R<sub>42</sub> represents hydrogen or alkyl;

 $R_e$ ,  $R_f$  and  $R_g$  represent, independently from each other, hydrogen or lower alkyl; and and n = 0, 1, 2, 3, 4, 5, or 6,

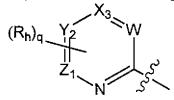
or an enantiomer, diastereoisomer, N-oxide, crystalline form, hydrate, solvate, pharmacologically active metabolite, prodrug, or pharmaceutically acceptable salt thereof.

41. (Previously presented) The method of claim 1 wherein said compound has a general formula III

$$A_1$$
— $L_1$ — $B_2$   $III$ 

wherein

A<sub>1</sub> is a 5-, 6- or 7-membered ring having the structure



wherein

W,  $X_3$ ,  $Y_2$  and  $Z_1$  together form a 3-5 membered chain, at least one of W,  $X_3$ ,  $Y_2$  and  $Z_1$  is a group  $(CR_h)_p$ , wherein p is 1 or 2; and the remainder of W,  $X_3$ ,  $Y_2$  and  $Z_1$  are each independently present or absent and when present are each independently C, C, C or C;

each R<sub>h</sub> is independently, halogen, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic, substituted or unsubstituted lower alkoxy, (lower)alkylcarbonyloxy, carboxyl, esterified carboxyl, amidated carboxyl, substituted or unsubstituted lower alkylthio, substituted or unsubstituted cycloalkyl, mercapto, nitro, carboxyl, carbamate, carboxamide, hydroxyl, ester, cyano, amine, amide, amidine, amido, sulfonyl, sulfonamide or N-(lower)-alkyl-N-phenylcarbamoyl wherein each nitrogen atom is independently unsubstituted or substituted independently with lower alkyl, lower alkoxy, halo or trifluoromethyl and wherein q is 0, 1, 2 or 3;

L<sub>1</sub> is substituted or unsubstituted alkenyl, alkynyl, or azo; and

B<sub>2</sub> is substituted or unsubstituted hydrocarbyl, substituted or unsubstituted cyclohydrocarbyl, substituted or unsubstituted heterocyclic, optionally containing one or more double bonds, or substituted or unsubstituted aryl,

wherein "substituted" refers to a radical wherein one or more hydrogen atoms has been replaced with a substituent selected from the group consisting of hydroxyl, alkyl, alkoxy, mercapto, aryl, heterocycle, halogen, trifluoromethyl, pentafluoroethyl, cyano, cyanomethyl, nitro, amino, N-substituted- or N,N-di-substituted amino, wherein one or both nitrogen atoms are substituted independently with alkyl, heterocycle, aryl which are each optionally further substituted independently with hydroxyl, alkyl or heterocycle, or, alkylamide, amidine, amido, carboxy, esterified carboxy, amidated carboxy, carboxamide, carbamate, ester, sulfonyl and sulfonamide groups, and the like,

- 42. (Original) The method of claim 41 wherein said administered compound is 3-(2-methylthiazol-4-yl)ethynylpyridine (MTEP).
  - 43. (Withdrawn) The method of claim 1 wherein said compound has a general formula IV

$$R_{45}$$
 $R_{45}$ 
 $R_{45}$ 
 $R_{44}$ 
 $R_{45}$ 
 $R$ 

wherein,

n is 0, 1 or 2;

X<sub>4</sub> is O, S, NH, or NOH;

R<sub>43</sub> and R<sub>44</sub> are each independently hydrogen, CN, COOR<sub>i</sub>, CONHR<sub>i</sub>, (C<sub>1-6)</sub>alkyl, or tetrazole, or R<sub>43</sub> and R<sub>44</sub> together represent an oxo group;

 $R_i$  is hydrogen or ( $C_{1-6}$ )alkyl;

R<sub>45</sub> is (C<sub>1-6</sub>)alkyl, (C<sub>2-6</sub>)alkenyl, (C<sub>3-8</sub>)cycloalkyl, -CH<sub>2</sub>OH, -CH<sub>2</sub>O-alkyl, or -COOH;

IV

Docket No.: 04266/100M275-US1

Ar<sub>I</sub> is an unsubstituted aromatic or heteroaromatic group or an aromatic or heteroaromatic group substituted with one or more substituent selected from the group consisting of  $(C_{1-6})$  alkylamino, di- $(C_{1-6})$ -alkylamino,  $(C_{1-6})$ alkoxy, carboxy, hydroxyl, cyano, halo, trifluoromethyl, nitro, amino,  $(C_{1-6})$ acylamino,  $(C_{1-6})$ alkylthio,  $(C_{1-6})$ hydroxyalkyl,  $(C_{1-6})$ alkylsulfonyl, and  $(C_{1-6})$ haloalkyl;

Z<sub>2</sub> represents a group of the formula

$$R_{46}$$
,  $R_{46}$ ,  $R_{46}$ ,  $R_{46}$ , wherein,

R<sub>46</sub> and R<sub>47</sub> are each independently from each other hydrogen, halogen, (C<sub>1-6</sub>)alkoxy, -OAr<sub>1</sub>, (C<sub>1-6</sub>)alkyl, -CF<sub>3</sub>, COOR<sub>i</sub>, CONHR<sub>i</sub>, -CN, -OH, COR<sub>i</sub>, -S-(C<sub>1-6</sub>)-alkyl, or -SO<sub>2</sub>-(C<sub>1-6</sub>)-alkyl;

 $A_2$  is  $CH_2$ , O, NH, NR<sub>i</sub>, S, SO, SO<sub>2</sub>,  $CH_2$ - $CH_2$ ,  $CH_2O$ , CHOH, or C(O), where  $R_i$  is as defined above;

 $B_3$  is CHR<sub>i</sub>, C(R<sub>i</sub>)<sub>2</sub>, (C<sub>1-6</sub>)alkyl, C(O), -CHOH, -CH<sub>2</sub>-O, -CH=CH, CH<sub>2</sub>-C(O), CH<sub>2</sub>-S, CH<sub>2</sub>-S(O), CH<sub>2</sub>-SO<sub>2</sub>, -CHCO<sub>2</sub>R<sub>i</sub>, or -CH-N(R<sub>i</sub>)<sub>2</sub>, where R<sub>i</sub> is as defined above; and Het is a heterocycle,

Docket No.: 04266/100M275-US1

or an enantiomer, diastereoisomer, N-oxide, crystalline form, hydrate, solvate, pharmacologically active metabolite, prodrug, or pharmaceutically acceptable salt thereof.

44. (Withdrawn) The method of claim 1 wherein said compound has general formula V-A

Ar<sub>2</sub>—G<sub>1</sub>—Ar<sub>3</sub>

V-A

wherein

Ar<sub>2</sub> is a heteroaryl group,

Ar<sub>3</sub> is an aryl group, where

Ar<sub>2</sub> and Ar<sub>3</sub> are each independently of each other optionally substituted with one or more substituents selected from the group consisting of -F, -Cl, -Br, -I, -OR<sub>j</sub>, -SR<sub>j</sub>, -SOR<sub>j</sub>, -SO<sub>2</sub>R<sub>j</sub>, -SO<sub>2</sub>NR<sub>j</sub>R<sub>k</sub>, -OCOR<sub>j</sub>, -OCONR<sub>j</sub>R<sub>k</sub>, -NRCOR<sub>k</sub>, -NRCO<sub>2</sub>R<sub>k</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>j</sub>, -CONR<sub>j</sub>R<sub>k</sub>, -C(O)R<sub>j</sub>, -CH(OR<sub>j</sub>)R<sub>k</sub>, -CH<sub>2</sub>(OR<sub>j</sub>), -R<sub>j</sub>, and -A-(CH<sub>2</sub>)<sub>n</sub>-NR<sub>j</sub>R<sub>k</sub>, wherein R<sub>j</sub> and R<sub>k</sub> are selected independently from the group consisting of H, CF<sub>3</sub>, (C<sub>1</sub>-<sub>10</sub>)alkyl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, heterocycloalkyl, aryl, or R<sub>j</sub> and R<sub>k</sub> may combine to form a C<sub>1-5</sub> methylene chain, and A is defined as CH<sub>2</sub>, O, NH, S, SO, SO<sub>2</sub> and n is 1, 2, 3, or 4,

G<sub>1</sub> is selected from the group consisting of -NH-, -S, -O-, -CO-, -CONH-, -CONHCH<sub>2</sub>-, -CH<sub>2</sub>CONH-, -CH<sub>2</sub>NHNH-, -CH<sub>2</sub>NHNHCH<sub>2</sub>-, -C=NO-CH<sub>2</sub>-, -CH<sub>2</sub>NHCH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>NH-, -NHCH<sub>2</sub>CO-, -NHCH<sub>2</sub>CHOH-, -NHCH<sub>2</sub>NHNH-, -NHCONH-, or G<sub>1</sub> is a cyclic group selected from the group consisting of cyclopentane, cyclopentadiene, furan, thiofuran, pyrrolidine, pyrrole, 2-imidazoline, 3-imidazoline, 4-imidazoline, imidazole, pyrazoline, pyrazolidine, imidazolidine, oxazole, 2-oxazole, thiazole, isoxazole, isothiazole, 1H-1,2,4-triazole, 1H-1,2,3-triazole, 1,2,4-oxathiazole, 1,3,4-oxathiazole, 1,4,2-dioxazole, 1,4,2-oxathiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1H-tetrazole, cyclohexane, piperidine, tetrahydropyridine, 1,4-dihydropyridine, pyridine, benzene,

Application No. 10/768,953 Amendment dated April 2, 2007

Reply to Office Action of January 24, 2007

tetrahydropyran, 3,4-dihydro-2*H*-pyran, 2*H*-pyran, 4*H*-pyran, tetrahydrothiopyran, 3,4-dihydro-2*H*-thiopyran, 2*H*-thiin, 4*H*-thiopyran, morpholine, thiomorpholine, piperazine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,2,3-triazine, 1,3,5-triazine, and 1,2,4,5-tetrazine groups,

Docket No.: 04266/100M275-US1

- 45. (Withdrawn) The method of claim 44 wherein Ar<sub>3</sub> is selected from the group consisting of phenyl, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl and benzonaphthenyl groups.
- 46. (Withdrawn) The method of claim 44 wherein Ar<sub>2</sub> is selected from the group consisting of thiazolyl, furyl, pyranyl, 2*H*-pyrrolyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazolyl, benzimidazolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl and chromenyl groups.
- 47. (Withdrawn) The method of claim 44 wherein Ar<sub>3</sub> is selected from the group consisting of phenyl, benzyl, naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl and benzonaphthenyl groups and Ar<sub>2</sub> is selected from the group consisting of thiazolyl, furyl, pyranyl, 2*H*-pyrrolyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzothiazolyl, benzimidazolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalizinyl, naphthyridinyl, quinazolinyl, cinnolinyl, isothiazolyl, quinoxalinyl, indolizinyl, isoindolyl, benzothienyl, benzofuranyl, isobenzofuranyl and chromenyl groups.
  - 48. (Withdrawn) The method of claim 1 wherein said compound has a general formula V-B

Application No. 10/768,953 Docket No.: 04266/I00M275-US1 Amendment dated April 2, 2007

Reply to Office Action of January 24, 2007

$$Ar_4$$
 $X_5$ 
 $Ar_5$ 
 $Y_3$ 
 $Z_3$ 
 $V-B$ 

wherein

 $X_5$ ,  $Y_3$ , and  $Z_3$  are independently selected from the group consisting of N, O, S, C, and CO wherein at least one of  $X_5$ ,  $Y_3$ , and  $Z_3$  is a heteroatom;

Ar<sub>4</sub> and Ar<sub>5</sub> are independently selected from the group consisting heterocyclic and fused heterocyclic groups containing 1 to 4 heteroatoms selected from the group consisting of N, O, and S and an aromatic group selected from the group consisting of phenyl, benzyl, 1-naphthyl, 2-naphthyl, fluorenyl, anthrenyl, indenyl, phenanthrenyl, and benzonaphthenyl, wherein Ar<sub>4</sub> and Ar<sub>5</sub> are optionally substituted with one or more substituents selected from the group consisting of -F, -Cl, -Br, -I, -OR<sub>j</sub>, -SR<sub>j</sub>, -SO<sub>2</sub>R<sub>j</sub>, -SO<sub>2</sub>NR<sub>j</sub>R<sub>k</sub>, -OCOR<sub>j</sub>, -OCONR<sub>j</sub>R<sub>k</sub>, -NRCOR<sub>k</sub>, -NRCO<sub>2</sub>R<sub>k</sub>, -CN, -NO<sub>2</sub>, -CO<sub>2</sub>R<sub>j</sub>, -CONR<sub>j</sub>R<sub>k</sub>, -C(O)R<sub>j</sub>, - CH(OR<sub>j</sub>)R<sub>k</sub>, -CH<sub>2</sub>(OR<sub>j</sub>)-R<sub>j</sub>, and -A-(CH<sub>2</sub>)<sub>n</sub>-NR<sub>j</sub>R<sub>k</sub>; wherein R<sub>j</sub> and R<sub>k</sub> are selected independently from the group consisting of H, CF<sub>3</sub>, (C<sub>1</sub>-<sub>10</sub>)alkyl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, heterocycloalkyl, aryl, or R<sub>j</sub> and R<sub>k</sub> may combine to form a C<sub>1-5</sub> methylene chain, A is defined as CH<sub>2</sub>, O, NH, S, SO, SO<sub>2</sub>,

and n is 1, 2, 3, or 4,

- 49. (Withdrawn) The method of claim 48 wherein said heterocyclic or fused heterocylic group is selected from the group consisting of quinolyl, quinazolyl, quinoxalyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, and pyrazyl.
- 50. (Withdrawn) A method of identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract in a mammal, comprising

Application No. 10/768,953 Docket No.; 04266/100M275-US1 Amendment dated April 2, 2007

Reply to Office Action of January 24, 2007

(a) determining the binding affinities of one or more test compound for an mGlu5 receptor and one or more of an mGlu1 receptor or Group II mGlu receptor;

- (b) identifying a test compound that
  - (1) binds to mGlu5 receptor with an affinity of at least 10<sup>-6</sup> M; and
  - (2) binds to mGlu5 receptor with an affinity at least 10-fold stronger than the affinity for mGlu1 receptor or Group II mGlu receptor.
- 51. (Withdrawn) The method of claim 50 further comprising

individually measuring the binding affinity of said one or more test compounds for one or more Group III mGlu receptor and

identifying a test compound that binds to mGlu5 receptor with an affinity at least 10-fold stronger than the affinity for a Group III mGlu receptor.

- 52. (Withdrawn) The method of claim 50 or 51 wherein step (b) comprises identifying a test compounds that
  - (1) binds to mGlu5 receptor with an affinity of at least 10<sup>-6</sup> M; and
  - (2) binds to mGlu5 receptor with an affinity at least 10-fold stronger than the affinity for each of mGlu1 receptor and Group II mGlu receptor.
  - 53. (Withdrawn) The method of claim 50 or 51 wherein step (b) comprises identifying a test compounds that
  - (1) binds to mGlu5 receptor with an affinity of at least 10<sup>-6</sup> M; and
- (2) binds to mGlu5 receptor with an affinity at least 100-fold stronger than the affinity for a mGlu1 receptor or Group II mGlu receptor.
- 54. (Withdrawn) The method of claim 53 wherein step (b) comprises identifying a test compounds that
  - (1) binds to mGlu5 receptor with an affinity of at least 10<sup>-6</sup> M; and

Docket No.: 04266/100M275-US1

(2) binds to mGlu5 receptor with an affinity at least 100-fold stronger than the affinity for each of mGlu1 receptor and Group II mGlu receptor.

- 55. (Withdrawn) The method of claim 50 or 51 further comprising measuring the ability of each of said identified test compound to act as an antagonist or inverse agonist at the mGlu5 receptor.
- 56. (Withdrawn) The method of claim 50 or 51 wherein said neuromuscular dysfunction is urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance, cystitis, incontinence, urine leakage, enuresis, dysuria, urinary hesitancy or difficulty in emptying the bladder.
- 57. (Withdrawn) The method of claim 56 wherein said neuromuscular dysfunction that is decreased urinary compliance is decreased bladder storage capacity.
- 58. (Withdrawn) The method of claim 56 wherein said neuromuscular dysfunction that is cystitis is interstitial cystitis.